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THE ONES TO WATCH

A PHARMA MATTERS REPORT.

OCTOBER–DECEMBER 2008

Expert review from Thomson Reuters of the most promising drugs changing clinical phase, receiving approval and launched this quarter, based on the strategic data and insight of *Thomson Pharma*[®], the world's leading pharmaceutical competitive intelligence solution.



As this edition of *The Ones To Watch* demonstrates, pharmaceutical innovators remain committed to their pipelines, no matter what the economic climate. Our lists this quarter include potential large-population treatments for cancer, HIV infection, asthma and osteoporosis, among others. But we also continue to see a number of promising niche, 'specialty' pharmaceuticals for small patient populations.

These specialty drugs might be the savior of the industry now that the blockbuster model seems a thing of the past. But there's a problem. Specialty drugs have a high cost per patient. As the economic pressures mount, payers may well decide to restrict standard benefits for these treatments—or exclude them from their schemes altogether.

Meanwhile, we're already seeing how the recession is making payers reluctant to supply brand drugs to their members when a cheaper generic is available. This is effectively forcing patients beyond their old worries about the safety and efficacy of generic drugs. If they're expected to pick up a greater share of the cost of their trusted brand, they may well be faced with the bald choice of abandoning their regime before treatment is complete (or attempting to use less than the prescribed dose), or taking the full course of a generic.

Indeed, as brand loyalty corrodes, even the words 'trusted brand' will no longer be spoken in the same breath as the familiar trademark names. Those lost sales will not suddenly shift back to the brands when the economy recovers.

It is in the face of sobering thoughts like this that we recognize just how optimistic the pharmaceutical industry can be. Developing new drugs is never merely a means to financial survival. It's an investment in the future—no matter how uncertain that future appears. So let's take a closer look at the five most promising drugs launched or receiving approval, and moving through each of the clinical phases, between October and December 2008.

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THE FIVE MOST PROMISING DRUGS LAUNCHED OR RECEIVING APPROVAL

DRUG	DISEASE	COMPANY
Lusedra™	Anesthesia care sedation	MGI Pharma
Mozobil™	Cancer	Genzyme
Zypadhera™	Schizophrenia	Eli Lilly
Promacta®	Idiopathic thrombocytopenia purpura	GlaxoSmithKline
TriLipix™	Mixed dyslipidemia	Abbott/Solvay

To induce general anesthesia for surgery and maintain sedation in intensive care units, many hospitals and out-patient settings turn to the intravenous drug propofol. Its worldwide sales in 1999 were estimated to exceed US\$750 million. However, the drug has a number of reported side effects, including reduced heart rate, decreased blood pressure, depressed respiration, elevated blood lipid levels, pain at the injection site, and the potential for bacterial contamination.

Many of these side effects may result from the product's formulation, which is composed of a non-soluble lipid-based emulsion. To solve the problems, MGI Pharma, a wholly-owned subsidiary of Eisai, developed [Lusedra™](#), a water-soluble prodrug of propofol which does not contain a lipid emulsion. Lusedra is converted rapidly into propofol by alkaline phosphatase enzymes in the body after intravenous injection.

Phase III trials, all of which had been conducted without an anesthesiologist present, were complete by March 2007. In the 252-patient bronchoscopy trial, patients were randomized to receive a control dose of 2 mg/kg fospropofol, or 6.5 mg/kg fospropofol. The sedation success rate was 88.7% in patients who received an initial bolus dose of 6.5 mg/kg fospropofol compared to 27.5% of patients on control. The safety profile was similar on both arms, and the most frequent adverse event was transient hypoxemia. Around 91.3% of patients on the higher fospropofol dose completed the procedure without the use of alternative sedative medication or ventilation, compared to 41.2% for control. Patients also indicated high satisfaction with the treatment.

In December 2008, the FDA approved Lusedra for monitored anesthesia care sedation in adult patients undergoing diagnostic or therapeutic procedures. Thomson Pharma forecasts sales of US\$90 million in 2011.

Turning to cancer, the first of several new treatments in this edition of *The Ones To Watch* is [Mozobil™](#) from Genzyme, one of a series of CXCR4 inhibitors for use as an injectable stem cell mobilizer for use in stem cell transplantation. The drug gained US approval for use in combination with granulocyte-colony stimulating factor (G-CSF) in stem cell transplantation in non-Hodgkin's lymphoma and multiple myeloma patients in December 2008.

In addition to its expected benefits for patients with these conditions, Genzyme believes the drug may also offer economic benefits to transplant centers. It claims the drug may decrease the number of apheresis days and provide transplant centers with predictable and efficient use of the apheresis center. Mozobil may also reduce the number of patients who require a second mobilization procedure due to a failure to mobilize sufficient numbers of cells with current therapy of G-CSF alone.

In June 2008, Genzyme declared that peak sales of the product in the transplant setting could reach US\$400 million annually. EU approval is expected in the second half of 2009, with approval in Australia and Brazil to follow. More than 1,000 patients have already received Mozobil through a compassionate use program in the US and through similar programs in Europe. Meanwhile, the drug is also in phase II development for the potential treatment of acute myelogenous leukemia.

We'll return to both non-Hodgkin's lymphoma and multiple myeloma later in this report.

Another notable drug moving through worldwide approvals is [Zypadhera™](#), a long-acting injection formulation of the oral atypical antipsychotic Zyprexa™ (olanzapine), developed by Eli Lilly for the maintenance treatment in adults with schizophrenia sufficiently stabilized during acute treatment with the standard formulation of the drug. Long-acting injection formulations have a number of benefits in treating long-term schizophrenia, where poor or partial treatment compliance is a major problem. Healthcare professionals know when patients have received their medication, and as soon as a patient fails to return for a scheduled injection. Unlike oral and short-acting injection formulations, long-acting injection formulations also allow for stable concentrations of the active ingredient to remain at a therapeutic range for an extended period of time.

Zypadhera comes on the back of Eli Lilly's success with Zyprexa, which was the sixth top-selling prescription pharmaceutical worldwide in 2007 (totaling US\$4.76 billion, a 9% year-on-year increase). These sales were achieved predominantly outside the US. The drug's showing in the US bestseller charts was significantly lower, despite the fact that antipsychotics are the third highest-selling therapeutic category in North America.

The pattern is repeated in the approvals for Zypadhera. Eli Lilly received approval for the drug in New Zealand in September 2008 (as Zyprexa Adhera™) and EU approval in December (as Zypadhera™). In the US, approval has been more rocky. The company made its initial filing in July 2007, but received a non-approvable letter from the FDA in February 2008. Eli Lilly submitted its complete response in July.

Thomson Pharma pencils in sales of more than US\$240 million in 2011.

In November 2008, GlaxoSmithKline celebrated the accelerated FDA approval of [Promacta®](#), an oral tablet formulation of a non-peptide, hematopoietic receptor agonist which mimics hematopoietic growth factors, including thrombopoietin, for the potential treatment of idiopathic thrombocytopenia purpura (ITP), chemotherapy-induced thrombocytopenia and hepatitis C virus infection-related thrombocytopenia.

It's the first such drug approved by the FDA, supported by an unanimous decision by the FDA's Oncology Drugs Advisory Committee on May 20, 2008, in which the panel voted 16-0 that Promacta demonstrates a favorable risk-benefit profile for the short-term treatment of patients with chronic ITP. *Thomson Pharma* forecasts sales for of more than US\$300 million in 2011.

We finish our review of newly approved or launched drugs with [TriLipix™](#), developed by Abbott in collaboration with Solvay. The company describes this as a "next-generation fenofibrate" PPAR alpha agonist, formulated as delayed-release capsules for the potential treatment of mixed dyslipidemia.

It received approval from the FDA in December 2008, for use in combination with a statin. TriLipix is notable as the first and only fibrate to be approved for use in this way. Filings in other territories are likely to follow. Meanwhile, a combined formulation of TriLipix and Crestor™ (rosuvastatin) is in phase III trials for lipid disorders, including hyperlipidemia, and Solvay has initiated phase II trials for diabetic macular edema.

THE FIVE MOST PROMISING DRUGS ENTERING PHASE III TRIALS

DRUG	DISEASE	COMPANY
GS-101	Corneal graft rejection	Gene Signal
Edoxaban	Atrial fibrillation	Daiichi Sankyo
Belinostat	Peripheral T-cell lymphoma	TopoTarget
VP-003	Acromegaly	Indevus
Justiva®	Scarring	Renovo

The most frequently-performed transplant surgery in the world is corneal grafts—more than 40,000 are performed every year to cure or prevent blindness. The procedure may therefore be routine, but donors are in short supply, there are long waiting lists (of up to two years), and the surgery comes with a high failure rate, as much as 35% over five years.

Commonly, the reason for graft failure is the body's own immune system. The cornea itself is normally avascular, but under certain circumstances new blood vessel creation can occur, inducing corneal graft rejection (CGR). There is currently no treatment to prevent this syndrome. Gene Signal hopes its candidate [GS-101](#), a topical eye drop or eye cream formulation of an insulin receptor substrate-1 (IRS-1)-inhibiting antisense oligonucleotide, will prove effective against CGR by blocking the pathways leading to the formation of blood vessels in the cornea.

In 2007, Gene Signal obtained Orphan Drug and Fast-Track status for GS-101 from the EMEA, in order to expedite its development of the drug against CGR, neovascular glaucoma (NVG) and retinopathy of prematurity (ROP). Phase III trials for CGR began in November 2008. The company is also trialing the drug for diabetic retinopathy, and developing a dermatological formulation of GS-101 for rosacea and psoriasis.

Atrial fibrillation (AF) is an irregular heartbeat, caused when the upper chambers of the heart beat inconsistently and rapidly. Patients with AF have a five times higher risk of having a stroke. Indeed, each year about 90,000 strokes are caused by AF in the US alone. What's more, these patients also tend to have more serious first strokes than patients without AF, resulting in higher mortality rates and longer hospital stays.

The current standard of care, the anticoagulant warfarin, poses potentially serious drug and food interactions and requires extensive monitoring. In May 2007, Daiichi Sankyo announced that its anticoagulant [edoxaban](#) (at the time of writing this name is provisional) was one of its top priority projects. This is a direct, orally active Factor Xa inhibitor, which the company hopes will prove effective against not just non-valvular AF but other cardiovascular indications including venous thromboembolism. Phase III trials for non-valvular AF began in December 2008.

The same month, we saw [belinostat](#), an injectable hydroxamate-type histone deacetylase inhibitor under development by TopoTarget, entering phase III trials for peripheral T-cell lymphoma (PTCL). This followed its award of Fast Track status by the FDA in June.

PTCL represents approximately a tenth of all non-Hodgkin's lymphomas in Western populations. Nearly all sufferers relapse after initial treatment with cytotoxic agents, and 5-year survival is extremely poor (less than 30%). A number of chemotherapy regimens are used for salvage therapy but there are currently no therapies approved specifically for the condition. Instead, primary treatment remains anthracycline-based regimens, predominantly the combination of cyclophosphamide, doxorubicin, vincristine and prednisone, to which PTCL generally responds poorly. We await further news from TopoTarget with interest.

Indevus, meanwhile, is developing [VP-003](#), a six-month subcutaneous implant formulation of the somatostatin analog peptide octreotide, for the potential treatment of acromegaly. This is a chronic hormonal disorder, generally of the middle-aged, that occurs when a pituitary tumor produces excess growth hormone, leading to enlargement of certain bones, cartilage, muscles, organs and other tissues. Indevus claims a target market of 18,000 patients in the US alone, with 1,000 new cases diagnosed each year.

The implant, developed using the company's Hydron drug delivery platform, is inserted in the inner aspect of the upper arm and is specifically designed to provide a continuous release of octreotide, suppressing release of growth hormone. Indevus is also investigating its use for the potential treatment of carcinoid tumors.

Phase III trials for acromegaly commenced in September 2008, with US launch slated for early 2011.

Long-term readers of *The Ones To Watch* may remember our mention of [Justiva](#)[®], an intradermal subcutaneous injectable recombinant TGF beta 3 formulation for the potential reduction of scarring. Back in January 2007, we reported that the candidate had just completed phase II efficacy trials in the UK, following Renovo's anti-scarring treatment Zesteem through its pipeline. Renovo still aims to be the first company to reach market with a pharmaceutical drug that can reduce scarring, and in June 2007 granted license for development and commercialization of Justiva outside the EU to Shire.

In December that year, Renovo announced the initial results of its phase II trials. Justiva met its primary endpoint, with significant efficacy under certain dosing regimens. Scars resulting from wounds treated with Justiva had an improved appearance compared with placebo-treated wounds on the same subject after 7 months. In April 2008, it reported 12-month data that again showed significant efficacy, particularly when given in two doses, one before and one after surgery, 24 hours apart.

Bolstered by these positive results, Renovo commenced a phase III trial for scar revision surgery in the EU in December 2008. The same month Shire announced plans to discuss a US phase III trial program with the FDA.

THE FIVE MOST PROMISING DRUGS ENTERING PHASE II TRIALS

DRUG	DISEASE	COMPANY
TNF α -kinoid	Crohn's disease	Neovacs
DNA prime, Modified Vaccinia Ankara boost vaccine	HIV infection	GeoVax
ACE-011	Osteoporosis	Accelaron Pharma/Celgene
Senicapoc	Asthma	Icagen
NXL-104	Infection	Novexel

Heading our survey of promising drugs entering phase II trials, [TNF \$\alpha\$ -kinoid](#) is a potential vaccine for TNF α -dependent autoimmune diseases such as rheumatoid arthritis and Crohn's disease. Developer Neovacs believes that a limited number of administrations of its candidate—3 or 4 per year—will be enough to control these diseases.

Anti-TNF α biological agents, which first appeared in the 2000s, have revolutionized the treatment of TNF α -dependent autoimmune diseases. Three drugs have reached the market so far, generating a combined turnover of almost US\$10 billion in 2007. A 2008 study by Pharmacor forecasts sales of close to US\$17 billion for all immunomodulators in 2017, of which US\$6 billion is for new products.

Phase I/II trials for Neovacs' vaccine in Crohn's disease began in October 2008. The drug is also in preclinical studies for rheumatoid arthritis.

Staying with vaccines, GeoVax is developing a [DNA prime, Modified Vaccinia Ankara \(MVA\) boost vaccine](#) based on multiple proteins, to protect against HIV infection. The company initiated a phase IIa trial of the vaccine in December 2008, following a grant of US\$15 million from the US National Institute of Allergy and Infectious Diseases (NIAID).

The vaccine comprises two DNA priming vaccines followed by a modified pox virus booster. In preclinical studies, it was shown that it does not prevent HIV infection as such, but primes the immune system's 'memory' and provokes a strong immune response, causing expression of the three major polyproteins, Gag, Pol and Env, that are expressed by HIV. This induces immune responses to all three proteins instead of only one or two, thus increasing the body's ability to recognize and react to HIV, controlling infection by keeping the virus from replicating in large numbers.

Maintaining a chronic, low-level infection prevents progression to AIDS and reduces the risk of virus transmission, since higher viral loads are associated with greater infectiousness. It is hoped that the drug may also be effective in treating people already infected.

The first of our two potential treatments for osteoporosis this quarter, [ACE-011](#) is a fusion protein based on the activin IIa receptor that inhibits signaling of the receptor, under development by Acceleron Pharma in collaboration with Celgene. It is hoped that the candidate will be an effective treatment of osteoporosis, cancer-related bone loss, and anemia.

It comes with high hopes. Preclinical studies demonstrated that ACE-011 has the potential not just to slow the rate of bone loss, but to rebuild bone even after substantial bone loss has already occurred. The drug significantly increased bone mineral density, improved bone architecture, increased bone formation rate and bone mechanical strength. Phase I clinical studies in healthy volunteers showed it also has an encouraging safety profile.

In January 2008, the Multiple Myeloma Research Foundation awarded Acceleron Pharma US\$1 million to develop ACE-011 for multiple myeloma-associated bone loss. Phase II trials for this condition began in October 2008.

We're pleased to highlight another promising treatment for asthma, this time [senicapoc](#) from Icagen. This novel, once-daily oral regimen is a potent and selective small molecule inhibitor of the Gardos channel, a calcium-activated potassium channel.

In phase I asthma trials, completed in July 2008, four cohorts of either 6 or 12 subjects received the drug for between 7 and 28 days, and were followed for 2 months after the last dose. The results showed that senicapoc was well tolerated with no serious adverse events, and had predictable and dose-proportional pharmacokinetics consistent with once-daily dosing. Phase II trials for allergic asthma began in October 2008, with data expected in 2009.

Due to mankind's increasing resistance to marketed antibiotics, there is a clear need for novel drugs that are active against multi-drug resistant bacteria. To address this, Novexel, spun out from sanofi-aventis in December 2004, is developing [NXL-104](#), an injectable non-beta lactam, beta-lactamase inhibitor, which it hopes will solve the problem of microbial resistance to beta lactam antibiotics (penicillins, cephalosporins, carbopenems) mediated by beta-lactamase enzymes in hospitals. As we reported in last quarter's *The Ones To Watch*, the global hospital antibiotic market is enormous, worth an estimated US\$15 billion in 2007.

Novexel believes NXL-104 is a significant advance since it is able to inhibit a broader range of beta-lactamases than currently marketed beta-lactam inhibitors. Its spectrum includes class A (including ESBL and KPC) and class C enzymes. In combination with ceftazidime, it will target infections caused by Gram negative bacteria, including Enterobacteriaceae and Pseudomonas. The company is also planning to study the drug in combination with imipenem. Phase II trials of NXL-104 with ceftazidime for complicated urinary tract infection began in November 2008.

THE FIVE MOST PROMISING DRUGS ENTERING PHASE I TRIALS

DRUG	DISEASE	COMPANY
CP-4126	Cancer	Clavis Pharma
VTX-2337	Cancer	VentriRx
Debio-0827	Neuropathic pain	Debiopharm
subcutaneous bisphosphonate and recombinant human hyaluronidase	Osteoporosis	Halozyme
AZD-1446	Age associated memory impairment	AstraZeneca/ Targacept

We begin our list of notable candidates entering trials this quarter with [CP-4126](#), under development by Clavis Pharma for the potential treatment of solid tumors. The company believes the oral tablets and capsules, which use its proprietary Lipid Vector Technology (LVT), constitute a novel agent against cancer.

In LVT, specific unsaturated lipids are chemically bound to existing, approved pharmaceuticals. Clavis's data suggest this results in improved efficacy, reduced side effects, and greater tissue penetration, among other benefits. In CP-4126, the existing drug in question is gemcitabine (Eli Lilly's Gemzar®), an established treatment for a number of cancers with sales of US\$1.6 billion in 2007. CP-4126 enables gemcitabine, available only as an intravenous injection, to be absorbed via the gut. This gives patients the potential benefit of home chemotherapy treatment, and could eliminate the costs of hospitalization.

In 2007, the US National Cancer Institute agreed to screen a number of Clavis's compounds in its NCI-60 test panel, including among them CP-4126. The candidate entered phase I trials in October 2008.

Cancer is also one of the diseases targeted by [VTX-2337](#), one of a series of toll-like receptor-8 (TLR8) agonists developed by VentriRx under license from Array BioPharma. Preclinical evaluation suggests that it may play a key role in augmenting the innate arm of the immune system, and provide value when used in combination with the standard of care.

Phase I trials began in December 2008 to assess the safety and pharmacology of multiple doses of VTX-2337 in patients with late-stage cancer. It's a significant step for VentriRx, which acquired exclusive worldwide rights to the TLR8 program in March 2007—its first clinical trial, and the first selective TLR8 agonist to reach the clinic.

Neuropathic pain is a major chronic pain condition, affecting as much as 6% of the world's population. Its causes range from shingles, herpes, and diabetes, to antiviral or antitumor chemotherapy surgery and low back disorders. The huge worldwide market, estimated to reach US\$5 billion by 2010, is still largely unaddressed: the pain does not respond well to usual painkillers.

Debiopharm hopes to make a difference with [Debio-0827](#), an oral dual inhibitor of aminopeptidase N and neutral endopeptidase. These enzymes are responsible for the rapid degradation of enkephalins, the body's endogenous opiates. By inhibiting the enzymes, Debio-0827 maintains a high level of enkephalins in the body, producing an analgesic effect as a response to pain. The drug entered phase I trials in October 2008.

Returning to osteoporosis, bisphosphonates are a class of molecules that bind to mineralized bone matrix and inhibit bone resorption. Currently, there are oral and intravenous bisphosphonates for the treatment of osteoporosis. Oral bisphosphonates require a cumbersome dosing regimen and can cause gastrointestinal side effects, a significant cause of patient non-compliance to prescribed therapy. Intravenous bisphosphonates mean that patients have to travel to an infusion center or see a specialist to receive their infusion.

Halozyme hopes to open a third channel to treatment with the first subcutaneous bisphosphonate. Currently, subcutaneous administration of bisphosphonates is not considered feasible due to injection-site toxicity in the skin and/or impractical injection volumes. Halozyme believes its combination of [subcutaneous bisphosphonate and recombinant human hyaluronidase](#) (rHuPH20) solves the problem, offering greater convenience, compliance and tolerability. The hyaluronidase increases the dispersion and systemic absorption of locally-injected drugs by temporarily degrading hyaluronan under the skin.

Phase I trials began in December 2008 to explore the combination's safety, tolerability and pharmacokinetics. Halozyme has not yet named the specific bisphosphonate, but preclinical studies were carried out with Novartis's Reclast® and Roche's Boniva®. The company is also investigating the combination for the potential treatment of skeletal metastases.

Lastly for this quarter, AstraZeneca and Targacept are investigating [AZD-1446](#) for the potential treatment of age associated memory impairment (AAMI), a common condition of normal aging characterized by gradual memory loss or other cognitive impairment. It currently has no approved treatment.

AZD-1446, an alpha-4 beta-2 neuronal nicotinic receptor (NNR) modulator, entered phase I trials in December 2008 to study its safety, tolerability and pharmacokinetics in single doses to healthy volunteers.

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